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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

file C/C

Office Action Summary	Application No. 09/068,293	Applicant(s) Sandalon et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Nov 3, 2000* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 2, 4-13, 16-20, 22-37, and 41-46* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4-13, 16-20, 22-37, and 41-46* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

1. Amendments to the claims filed on November 3, 2000 in Paper No. 11 have overcome the objection to claims 1 and 6.

2. Amendments to the claims filed on November 3, 2000 in Paper No. 11 have overcome the rejection of claims 1-46 under 35 USC 112, first paragraph, scope of enablement regarding the combination of VP1, VP2 and VP3 for capsid formation (item 14 in the previous office action) is withdrawn.

3. Amendments which deleted the limitation of therapy in claims 41-42 and 46 have overcome the rejections under 35 USC 112, first paragraph and the rejections are withdrawn.

4. Arguments regarding the rejection of claims 1-17 and 35-46 under 35 USC 112, first paragraph over the limitation of the claims to antisense nucleic acids and ribozymes is found convincing and the rejection is withdrawn.

5. All rejections to the claims under 35 USC 112, second paragraph have been overcome by amendment except for one item regarding claim 1 which is repeated below. The new claim language presented in claims 7, 10, 12, 25, 28 and 32 is clear and unambiguous. The examiner's interpretation of the claims set forth in the previous office action no longer applies, and is therefore withdrawn.

6. Arguments regarding the remaining rejections of the claims under 35 USC 112, first paragraph, 102 and 103 have not been found convincing, and the responses to the arguments are set forth in the rejections below.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**.

Claim Objections

8. Claim 13 is objected to because of the following informalities: A comma should be placed after "is antisense RNA or DNA" in line 2. Appropriate correction is required.

9. Claim 27 is objected to because of the following informalities: The word "a" should be inserted before "DNA" in line 3 for grammatical reasons. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 2, 4-8, 10-13, 16-20, 22-26, 28-37 and 41-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification at pages 19-20 makes clear the

necessity of having an *ori* sequence in each nucleic acid which is encapsidated in the claimed SV40 protein capsid structures. Since claims 9 and 27 specifically recite that the DNA sequence comprises said *ori* sequence, this makes it clear that the claimed subject matter of claims 1-8, 10-26 and 28-46 are therefore contemplated as **not** having an *ori* sequence, which as stated above is taught against by the instant specification.

Response to Arguments

12. Arguments set forth in Paper No. 11 assert that the *ori* is not necessary for *in vitro* packaging of DNA in SV40 capsids. Reference is made to page 20 of the instant specification at lines 23-35 to support the assertion. Attention is drawn to lines 19-22 where it states "[a]n additional important advantage is that the *ses* element is not required for *in vitro* packaging (Tables 2 and 3), reducing the size of the required SV40 sequences to about 100bp, comprising the *ori*". This statement is abundantly clear that the *ori* is required for *in vitro* packaging. If the suggested data can be provided to the contrary, using the teachings of the instant specification as guidance, it will be carefully considered.

13. Claims 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to therapeutic methods of using the construct of SV40 viruses or pseudoviruses comprising exogenous nucleic acid and at least one pure or semi-purified SV40 capsid protein. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve experimentation with SV40 constructs *in vivo* to demonstrate therapeutic activity of the constructs.

b- Applicants have provided guidance and working examples of the constructs *in vitro* and no working examples and only limited prophetic guidance for therapeutic use of the constructs *in vivo*.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the

developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

14. Arguments set forth in Paper No. 8 assert that the references provided with the response show that the claims are enabled. The references provided in the response of Paper No. 8 have publication dates after the priority filing date of the instant application, and may not be used as proof of enablement. Therefore the arguments are moot.

15. Arguments set forth in Paper No. 11 assert that claims 43 and 44 have been amended to remove limitations to gene therapy. Claims 43 and 44 are drawn to methods of delivery of a

nucleic acid to a patient. Treatment of a patient with a nucleic acid constitutes gene therapy. Therefore the claims continue to be rejected under 35 USC 112, first paragraph, above. Should such limitations be removed in future amendments, a reconsideration of the instant rejection would be made at that time, based on the language presented in the amendment.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1, 2, 4-13, 16, 17 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claim 1 is rejected because of an internal inconsistency. Section "e)" in the Markush Group states that the "constituent" is an "exogenous protein or peptide product". There is no provision in section "e)"for a DNA as required by the preamble. Therefore, the "DNA construct" of the claim is left without a DNA element as the limitations of section "e)" are applied to the claimed "DNA complex".

Response to Arguments

19. Arguments set forth in Paper No. 11 regarding this rejection have been considered, but are not found convincing because claim 1 recites a "DNA complex" in the preamble, but amended language of section "e)" fails to provide for a DNA in the complex.

20. Claims 2, 4-13, 16, 17 and 41 recites the limitation "complex". There is insufficient antecedent basis for this limitation in the claim. The insertion of "DNA" before "complex" would cure this defect.

21. Claims 45 and 46 recite the limitation "active ingredient". Amendments to the claims have resulted in a new interpretation of this term. The term "active ingredient" is understood by those in the pharmaceutical arts, but the present context reads more broadly than just the pharmaceutical arts and as such does not have a clear and well defined meaning in its present context. This limitation is not defined by the claims or specification. Therefore, the term is vague and indefinite.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1, 2, 4-7, 9, 10, 12, 16-20, 22-25, 27-34, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Christensen et al (of record).

Christensen et al. taught (see especially the abstract, the introduction, the figures, pages 438-439 and the discussion) a method of construction of SV40 viruses and pseudoviruses (infectious aggregates) comprising a semi-purified or pure SV40 VP1 capsid protein and at least

one other SV40 capsid protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses (infectious aggregates). The pseudoviruses (infectious aggregates) were treated with nuclease to remove non-packaged DNA. The DNA was circular or linear.

Response to Arguments

24. Arguments set forth in Paper No. 8 assert that Christensen et al. do not teach exogenous DNA. Christensen et al. taught at page 433, column 2, "assembly was attempted using an exogenous source of viral DNA, i.e., SV 40 nucleoprotein complex (White and Eason, 1971), and empty virion shells." Therefore, the DNA of Christensen et al. fulfills the limitations as set forth in the claims. Other arguments set forth relate to limitations which are not claimed, and as such, are not relevant to the issues of the rejection.

25. Arguments set forth in Paper No. 11 assert that Christensen et al. taught "infectious aggregates" instead of viruses and pseudoviruses. While the nomenclature of Christensen et al. differs from the instant claimed nomenclature, the "infectious aggregates" of Christensen et al. meet all of the limitations of the instant claimed invention, where the "infectious aggregates" of Christensen et al. contained an exogenous DNA, a semi-purified SV40 VP1 capsid protein and a mixture of at least one other SV40 capsid protein where the resultant (viral particles) "infectious aggregates" contained an origin of replication and may be expressed.

26. Arguments set forth in Paper No. 11 assert that the DNA of Christensen et al. was "nucleoprotein", not naked DNA. "Naked DNA" is not claimed, and as such the point is moot.

Adding a limitation which makes this distinction may, however, avoid the instant anticipatory rejection.

27. Claims 1, 2, 4-7, 9, 10, 12, 16-20, 22-25, 27-34, 41 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Colomar et al. (of record, "AS").

Colomar et al. taught (see especially the abstract, the introduction, materials and methods, the figures and the discussion) a method of construction of SV40 viruses and pseudoviruses comprising a semi-purified or pure SV40 capsid protein and at least one other SV40 protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses. The pseudoviruses were treated with nuclease to remove non-packaged DNA. The DNA was circular or linear.

Response to Arguments

28. Arguments set forth in Paper No. 11 assert that Colomar et al. did not use "exogenous DNA". In the abstract, in the materials and methods section and at page 2784, column 1 Colomar et al. taught the use of polyoma virus DNA in place of SV40 DNA. It is further asserted that the viral particles of Colomar et al. were "imperfect". This is not a claim limitation, and as such is not germaine to the rejection.

29. Arguments set forth in Paper No. 11 assert that the reassembled viral particles of Colomar et al. did not use SV40 VP1 capsid protein in combination with other SV40 capsid proteins to make their reassembled viral particles. Colomar et al. taught (see especially the discussion on

page 2784) that the reassembled viral particles contained SV40 VP1 capsid protein and other SV40 capsid proteins.

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. Claims 1, 2, 4-13, 16-20, 22-37 and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen et al. or Colomar et al. (above) each in view of Carswell et al. (of record), Oppenheim et al. (J. Virol. Vol. 66, 1992, of record) and US Pat No. 5,863,541.

Christensen et al. or Colomar et al. each taught the invention described above. Also claimed is that the exogenous nucleic acid may be RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone.

Christensen et al. or Colomar et al. did not teach the exogenous nucleic acid may be RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone.

US Pat No. 5,863,541 taught (see especially the abstract, the summary, column 5 and the claims) the production of AAV capsid proteins which were allowed to self assemble into capsids and then the exogenous nucleic acid was added to give pseudoviruses. The exogenous nucleic

acid may be DNA, RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone. The host cell may be a human cell.

Carswell et al. taught (see especially the abstract) the advantage of combining an SV40 agnoprotein with SV40 capsid proteins to facilitate the assembly of capsids.

Oppenheim et al. (see especially the abstract) taught the advantage of combining an SV40 ori sequence with SV40 capsid proteins to facilitate the assembly of capsids.

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of Christensen et al. or Colomar et al. with the method of US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because the capsids proteins of US Pat No. 5,863,541 were assembled in a like manner to the instant claimed invention, and inclusion of nucleic acids which encode various entities is an obvious extension of the gene therapy teachings of Christensen et al. or Colomar et al. and because the AAV capsids of US Pat No. 5,863,541 were used for the same purpose and demonstrated the generally accepted practice of making pseudovirions for delivery of exogenous nucleic acids and proteins to cells. It is assumed that the making of AAV pseudovirions and SV40 pseudovirions is equivalent for the purpose of delivering exogenous nucleic acids and proteins to cells. Carswell et al. and Oppenheim et al. merely taught well known and advantageous methods of facilitating the assembly of SV40 capsid proteins into SV40 capsids.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the method of Christensen et al. or Colomar et al. with the method of

US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because US Pat No. 5,863,541 recited at column 3, lines 11-13, "[m]olecules which may be associated with or encapsidated into capsids include DNA, RNA, proteins, peptides, small organic molecules, or combinations of the same.", continuing at lines 26-27, "[t]his system may be particularly advantageous in AAV gene delivery systems...". Then at column 4, lines 21-23, "[m]ethods for the *in vitro* construction of AAV capsids and for the *in vitro* packaging of these capsids are also provided." Colomar et al. recite at page 2785, column 2 "[t]hese experiments show that it is possible to reconstitute *in vitro* infectious virus-like particles". Therefore, the capsids of US Pat No. 5,863,541 and Christensen et al. or Colomar et al. were intended for the same purpose, where US Pat No. 5,863,541 utilized AAV capsids and Christensen et al. or Colomar et al. utilized SV40 capsids. Carswell et al. and Oppenheim et al. merely taught well known and advantageous methods of facilitating the assembly of SV40 capsid proteins into SV40 capsids. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Christensen et al. or Colomar et al. with Carswell et al., Oppenheim et al. and US Pat No. 5,863,541.

Response to Arguments

32. Arguments set forth in Paper No. 8 assert that the AAV capsids of US Pat No. 5,863,541 are different from the instant SV40 capsids, and the comparison is invalid. US Pat No. 5,863,541 is relied upon here to show a well known use of capsid proteins to encapsidate foreign nucleic acids including antisense.

33. In response to applicant's arguments in Paper No. 8 against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

34. In response to applicant's argument in Paper No. 8 that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the references are justifiably combined since each of US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. was used to demonstrate well known and obvious elements which are used to study related subject matter as the instant SV40 virion encapsidation.

35. Arguments set forth in Paper No. 11 assert that there is no motivation to combine US Pat No. 5,863,541 with the primary references since US Pat No. 5,863,541 dealt exclusively with the use of AAV capsids, and does not teach the use of SV40 capsids for this purpose. US Pat No. 5,863,541 is used in the rejection to demonstrate that the inclusion of nucleic acids such as antisense nucleic acids and ribozymes into the capsids of viral particle for the purpose of introduction into a cell was well known to those of skill in the art. In support of this position, US Pat No. 6,107,062, filed on July 30, 1992 taught (see the summary at columns 4-5) the general

use of capsids for the transport of antisense nucleic acids and ribozymes into cells which further supports the motivation to combine, and demonstrates the well known use of any viral capsid to introduce nucleic acids into a cell.

36. Claims 14 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen et al. or Colomar et al. each with Carswell et al., Oppenheim et al. and US Pat No. 5,863,541. as applied to claims 1, 2, 4-13, 16-20, 22-37 and 41-46 above, and further in view of Szczylik et al. (of record).

The claims are rejected for all the reasons above and because Szczylik et al. taught (see especially the abstract, materials and methods and the figures) an antisense oligonucleotide to *bcr/abl.*

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. and US Pat No. 5,863,541 with the antisense oligonucleotide of Szczylik et al. to produce the instant invention because Forstova et al. or Christensen et al. with US Pat No. 5,863,541 taught the inclusion of antisense oligonucleotides in the assembled SV40 pseudocapsids. The antisense oligonucleotide of Szczylik et al. being an obvious choice of one of the many antisense oligonucleotides within the purview of one of ordinary skill in the art at the time of the instant invention.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. and US Pat No.

5,863,541 with the antisense oligonucleotide of Szczylik et al. to produce the instant invention because the antisense oligonucleotide of Szczylik et al. was an obvious choice of one of the many antisense oligonucleotides within the purview of one of ordinary skill in the art at the time of the instant invention. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Forstova et al. or Christensen et al. with US Pat No. 5,863,541 and with Szczylik et al.

Conclusion

37. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

38. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the

examiner by telephone are unsuccessful, the examiner's supervisor, Richard Schwartz can be reached at (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.
Examiner
February 7, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER